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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/560,124	04/28/2000	Ralph A. Nixon	50122/002003	3388

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EXAMINER
BAKER, ANNE MARIE

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/08/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)	
09/560,124	NIXON ET AL.	
Examiner	**Art Unit**	
Anne Baker	1632	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *1-15 and 32-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-31 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The response filed April 8, 2002 (Paper No. 6) has been entered. The Certificate of Mailing dated November 5, 2001 is acknowledged. Applicants' election with traverse of Group II, Claims 16-31 and 35 in Paper No. 6 is acknowledged. The elected invention is drawn to a method for identifying a compound useful for the treatment of Alzheimer's disease using a rab5 transgenic mouse or cells. The traversal is on the grounds that Groups I, II, and III share classification (page 2, paragraph 1 of the response). This is not found persuasive because the shared classification does not preclude the necessity to perform separate searches. Each distinct transgenic mouse requires a separate search and each must be considered separately for examination purposes. Despite the shared classification, the inventions are patentably distinct because they involve the use of distinct transgenic animals that are not obvious variants. Class 800, subclass 18 covers transgenic mice and includes a wide variety of transgenic mice. The class and subclass designation does not imply relatedness beyond this very large and broad category. Thus, similar classification is not sufficient criteria to demonstrate that the required search would be the same for separate inventions that are similarly classified. In the instant case, each of the transgenic mice used in the methods of the inventions of Groups I-V are distinct animals. Each transgenic animal is made using a different method and each would be expected to have a unique phenotype. The transgenic animals are not obvious variants. Thus, one transgenic animal would not be considered obvious over any of the others. Therefore, the methods of the inventions of Groups I-V are each drawn to mutually exclusive methods that require the use of different starting materials and produce different effects. The methods are patentably distinct and a search for the method of Group II would not identify art relevant to Groups I and III-V. Therefore, additional searching would be required to cover the inventions of Groups I and III-V. Because the searches are not coextensive, a search and examination of all five patentably distinct inventions would constitute a serious burden on the Examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-35 are pending in the instant application.

Claims 16-31 embrace the invention of Groups II-IV. Claim 35 embraces the invention of Groups I-IV. However, Claims 16-31 and 35 will be examined only to the extent that they encompass the elected subject matter. The claims should be amended to reflect the elected invention.

Claims 1-15 and 32-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **with** traverse in Paper No. 6.

Claims 16-31 and 35 are examined herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-20 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method for identifying a candidate compound as a compound that may be useful for the treatment of Alzheimer's disease (AD), using cells expressing a recombinant nucleic acid encoding rab5, wherein the method is carried out *in vitro* (i.e., in cells in culture), does not reasonably provide enablement for an *in vivo* method for identifying a compound that may be useful for the treatment of AD, using a transgenic mouse expressing a transgene comprising a recombinant nucleic acid encoding rab5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method for identifying a candidate compound as a compound that may be useful for the treatment of AD. The method involves providing a cell expressing a recombinant nucleic acid encoding rab5, contacting the cell with the candidate compound, and measuring the activity of the endocytic pathway. The claims cover *in vitro* and *in vivo* applications of the method. Claims 27-31 and 35 are exclusively directed to methods of using transgenic mice in identifying a candidate compound as a compound that may be useful for the treatment of AD.

The specification fails to provide an enabling disclosure for a transgenic mouse expressing a transgene comprising a recombinant nucleic acid encoding rab5 because the phenotype of a transgenic animal is unpredictable. The specification teaches and the claims require that *in vivo* overexpression of rab5 must result in increased activity of the endocytic pathway. However, the state of the art is such that the phenotype of an transgenic animal is unpredictable. For the reasons discussed below, it is not a routine matter to obtain expression of a transgene at the requisite level, at the appropriate time, in the desired tissue, to produce a desired effect, i.e. a particular phenotype (in this case, increased activity of the endocytic pathway), using any transgene construct as recited in the claims.

The specification fails to provide an enabling disclosure for a transgenic mouse of the type recited in the claims. The transgenic mouse is an essential element of the claimed invention. However, the mere capability to perform gene transfer in a given species is not enabling for the rab5 transgenic mice because the desired phenotype cannot be predictably achieved simply by introducing a transgene construct of the type recited in the claim. While gene transfer techniques are well-developed for a number of species, especially the mouse, methods for achieving the desired level of transgene expression in appropriate tissues are less well-established. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or retrovirus-mediated gene transfer. However, the state of the art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. Insertional inactivation of endogenous genes and position effects

(see Wall, 1996, p. 61, paragraph 3) can dramatically influence the phenotype of the resultant transgenic mouse. Integration of the transgene near highly active genes or, alternatively, in a transcriptionally inactive region, can influence its level of expression. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic mammal depends on the particular gene construct used, to an unpredictable extent. The particular genetic elements required for appropriate expression varies from species to species. Thus, constructs that use heterologous genetic elements will not always confer the desired phenotype in a mouse. Wall (1996) reports that our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (p. 61, paragraph 3). This is especially relevant for the use of genetic elements from species in which genetic studies are less advanced than in the mouse. Thus, the species-specific requirements for transgene design introduces an additional level of unpredictability associated with the development of transgenic mice. Even differences in the genetic background of transgenic mice can have an unpredictable effect on phenotype (Sigmund, 2000). In the absence of specific guidance, the production of a transgene-dependent phenotypic alteration resulting from the introduction of a nucleic acid construct as recited in the claim, is unpredictable. The phenotype depends on the particular transgene construct used, to an unpredictable extent. In the absence of specific guidance, one skilled in the art would not know how to make a rab5 transgenic mouse that exhibits increased activity of the endocytic pathway, appropriate for use in the claimed method of compound screening, without undue experimentation.

The species-specific requirements for transgene design are not clearly understood. Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins et al. (1990) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer et al. (1990) describe spontaneous inflammatory disease in inbred Fischer and

Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins et al., 1989; Taurog et al., 1988) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats.

In view of the limited guidance in the specification, the lack of working examples for rab5 transgenic mice, the unpredictability in the transgenic art, and the broad scope of the claims, one skilled in the art would have been required to engage in undue experimentation in order to practice the claimed method over the full scope.

Claims 27-31 and 35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to methods of using rab5 transgenic mice in identifying a candidate compound as a compound that may be useful for the treatment of AD. The claims are exclusively directed to *in vivo* methods of compound screening.

For the reasons discussed above, the specification fails to provide an enabling disclosure for methods of using a rab5 transgenic mice in compound screening.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16-31 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 16-31 and 35 are directed to non-elected subject matter. Applicants elected Group II. However, Claims 16-31 embrace the inventions of Groups II-IV and Claim 35 embraces the invention of Groups I-IV. Thus, the metes and bounds of the claims are not clearly set forth.

Claims 16-31 and 35 are indefinite in their recitation of "a compound that is useful for the treatment of Alzheimer's disease" because the assay does not provide a demonstration that the compound is actually useful for the treatment of Alzheimer's disease, but rather only provides an initial screening of compounds that may be useful for the treatment of Alzheimer's disease. Use of the claim language "a compound that may be useful for the treatment of Alzheimer's disease" is recommended.

Claim 17 is indefinite in its recitation of "said activity of the endosomal pathway" because the phrase lacks antecedent basis. Use of the phrase "said activity of the endocytic pathway" is suggested.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Anne-Marie Baker, Ph.D.

Anne-Marie Baker
ANNE-MARIE BAKER
PATENT EXAMINER